

children. Although the cost of development would be high, at present this is the most promising approach toward control of the acute respiratory diseases.

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The authors are associated with the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.

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III. MYXOVIRUSES: PARAINFLUENZA

*Robert H. Parrott, M.D.; Andrew J. Vargosko, Ph.D.; Hyun Wha Kim, M.D.; Joseph A. Bell, M.D., Dr.P.H., F.A.P.H.A.; and Robert M. Chanock, M.D.*

PARAINFLUENZA viruses, of which there are four types, are members of the myxovirus group, and they are immunologically distinct from influenza and other myxoviruses.<sup>1,2,3,4,4a</sup> Most of the information on these agents, including the original uncovering of Types 3 and 4, has become available because certain erythrocytes adsorb to the surface of monkey kidney tissue culture cells infected with these viruses.<sup>5</sup> This phenomenon is called hemadsorption. Recovery of parainfluenza viruses was facilitated by the hemadsorption technic since many naturally occurring strains failed to produce a cytopathic effect during initial tissue culture passage. In

fact cytopathic effects with Types 1 and 4 viruses are minimal even with well adapted strains.<sup>1,3</sup> After isolation, parainfluenza viruses were identified by the use of type-specific rabbit antisera in a hemadsorption inhibition test.<sup>1</sup> In our studies a modified Bengtson method complement-fixation test<sup>6</sup> was used for serological diagnosis and a fourfold rise in antibody was considered evidence for infection.

Sensitivity of Serological Methods

The complement-fixation test was quite sensitive in detecting evidence of infection but, particularly with human

**Table 1—CF Antibody Response of Infants and Children from Whom Parainfluenza Viruses Recovered**

Parainfluenza Virus Recovered	No. Test	Antibody Rise (4× or Greater)						
		Only	Homotypic			Total (%)	Hetero- typic Only	Total (%)
			+ Heterotypic					
			Type 1	Type 2	Type 3			
Type 1	41	16	—	2	13*	30 (73%)	2	32 (78%)
Type 2	11	4	0	—	3	7 (64%)	1	8 (73%)
Type 3	28	18	3	0	—	21 (75%)	1	22 (79%)
Total	80	38	3	2	16*	58 (72%)	4	62 (78%)

\* One had double rise with Type 2.

**Table 2—Recovery of Parainfluenza Viruses from Various Respiratory Disease Syndromes; October, 1957-June, 1961**

Category	No. Tested	Percentage Recovery of Virus			
		Type 1	Type 2	Type 3	Total
Croup	206	20.0	4.4	4.4	29.0
Broncho- pneumonia	697	0.6	0.1	1.6	2.0
Bronchiolitis	321	1.0	0.3	4.0	5.0
Severe bronchitis and pharyngitis	706	1.0	0.4	2.0	3.2
Rhinitis, pharyngitis, bronchitis	2,746	2.4	0.3	3.0	6.0
Total respiratory cases	4,676	2.7	0.5	2.8	6.0
Control cases	2,946	0.2	0.03	0.2	0.5

serums, there were cross-reactions among the various parainfluenza types (Table 1). For example, of 80 children from whom parainfluenza viruses 1, 2, or 3 were recovered, a complement-fixing antibody rise to some parainfluenza virus was noted in 78 per cent. In 72 per cent a homotypic antibody rise was detected; heterotypic antibody rises

were also noted, particularly with parainfluenza 3 antibody during convalescence from parainfluenza 1 or 2 infection. This is probably due to the fact that these viruses share antigens.<sup>1,4a</sup> Parainfluenza 3 infection is extremely prevalent and usually occurs earlier in life than does parainfluenza 1 or 2 infection. Thus, the antibody forming mechanism

is frequently conditioned to parainfluenza 3 virus at the time when Type 1 or 2 infection occurs.

#### Association with Illness: Virus Recovery

In our cross-sectional studies from October, 1957, to June, 1961, oropharyngeal specimens from 7,622 children were studied, and we recovered 132 parainfluenza 1, 23 parainfluenza 2, and 136 parainfluenza 3 virus strains. As shown in Table 2 these viruses were recovered from 6 per cent of 4,676 children with some type of respiratory tract illness and from 0.5 per cent of 2,946 control children free of respiratory disease at the time of sampling. For each of the virus types there was at least a twelvefold greater percentage virus recovery from children with respiratory tract illness over controls without respiratory disease. Thus, by virus recovery data, the association of parainfluenza viruses 1, 2, and 3 with respiratory tract illness in children has been demonstrated.

Parainfluenza 1 and 3 viruses were almost equally frequently recovered from the large group of children with rhinitis, pharyngitis, and bronchitis coming to the outpatient department; parainfluenza 1 virus from 2.4 per cent, and parainfluenza 3 from 3 per cent. However, in the more severe lower respiratory tract illness, parainfluenza 1 infections were most closely identified with croup (20 per cent) whereas the parainfluenza 3 infections were associated with bronchopneumonia and bronchiolitis more often than parainfluenza 1 infections. Parainfluenza 2 virus was much less frequently isolated than either parainfluenza 1 and 3 and did not often seem to be associated with illness other than croup.

#### Association with Illness: Serological Studies

Serological studies both confirmed the association of parainfluenza viruses with illness and highlighted their contribution to the various clinical syndromes

**Table 3—Serologic Evidence of Parainfluenza Infection in Infants and Children with Respiratory Disease Admitted to the Hospital; October, 1957-June, 1961**

Category	Mean Age (Mo)	No. Tested	Percentage with CF Antibody Rise			Total
			Type 1	Type 2	Type 3	
Croup	26	154	21.0	8.0	10.0	40
Bronchopneumonia	28	511	4.0	0.6	12.0	16
Bronchiolitis	12	227	1.0	—	12.0	13
Severe bronchitis and pharyngitis	37	521	4.0	2.0	13.0	19
Total respiratory cases	28	1,413	5.0	2.0	12.0	19
	Age (Mo)					
	0-24	246	0.8	0.4	4.9	6
Control cases	0-48	437	1.1	0.9	4.1	6
	0-60	511	1.0	1.0	3.9	6
	0->60	670	0.7	0.9	3.1	5

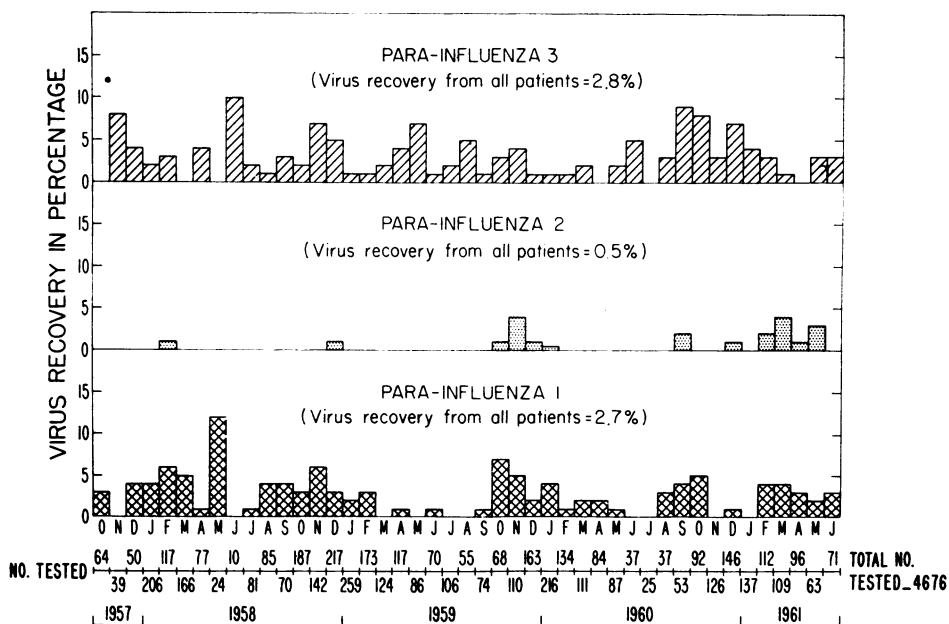


Figure 1—Recovery of Parainfluenza Viruses from Patients with Respiratory Illness by Month

(Table 3). Thus, 19 per cent of children with respiratory tract illness requiring hospitalization had a rise in antibody to parainfluenza viruses as contrasted with 5 per cent of controls in comparable age groups. This relatively high frequency of antibody rise, especially to parainfluenza 3 virus, among hospitalized children without respiratory tract illness suggests both that parainfluenza 3 infection spreads readily among individuals living close together and that infection may occur in the absence of illness.

By serological evidence parainfluenza 3 infection was more common (12 per cent of total respiratory tract illness) than parainfluenza 1 infection (5 per cent of total respiratory tract illness). The association of parainfluenza 1 with croup and parainfluenza 3 with bronchopneumonia, bronchiolitis, croup, and bronchitis was again evident. Parain-

fluenza 2 infection again was associated principally with croup. Totally, 40 per cent of the croup cases, 16 per cent of bronchopneumonia cases, 13 per cent of bronchiolitis cases, and 19 per cent of those with severe bronchitis and pharyngitis were associated with one of these three parainfluenza viruses.

### Prevalence in Time

Over 3 and  $\frac{3}{4}$  years (Figure 1) parainfluenza 1 and 3 viruses have been recovered in each year, in every season, and in virtually every month. Parainfluenza 2 viruses have been recovered more sporadically. Serologic evidence of parainfluenza infection confirmed the high prevalence of these viruses (Figure 2). The almost continuous presence of parainfluenza 1 and 3 infection contrasted with the sporadic occurrence, for example, of influenza infection.

Figure 2—Serologic Evidence of Parainfluenza Infection by Month (Contrasted with Influenza Infection)

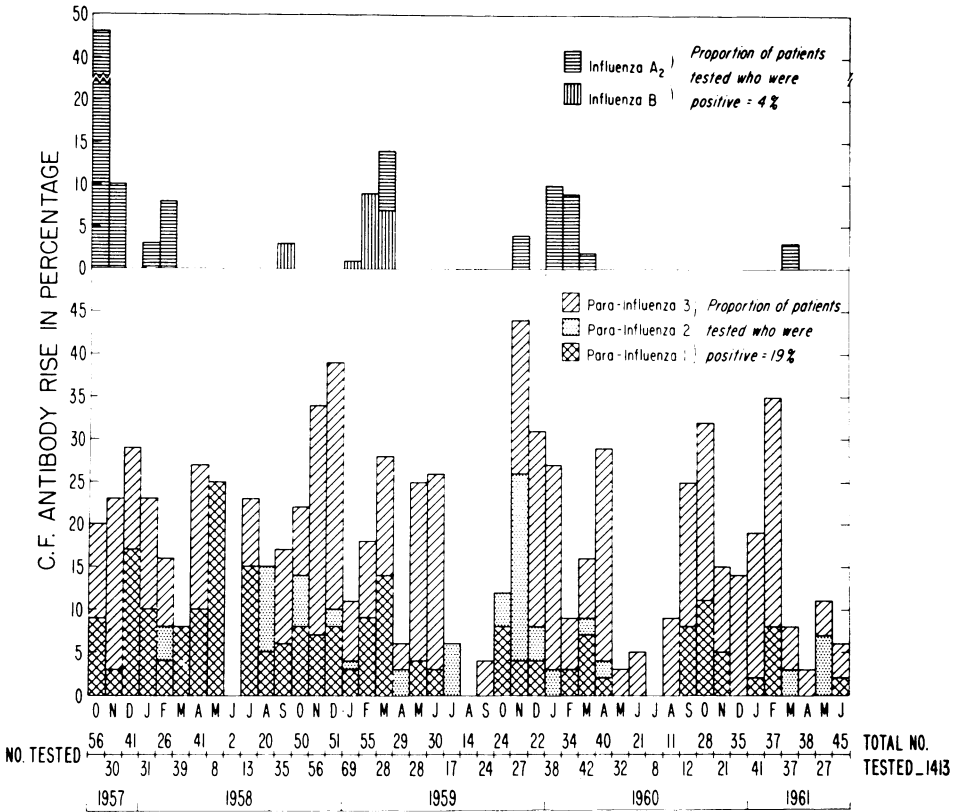
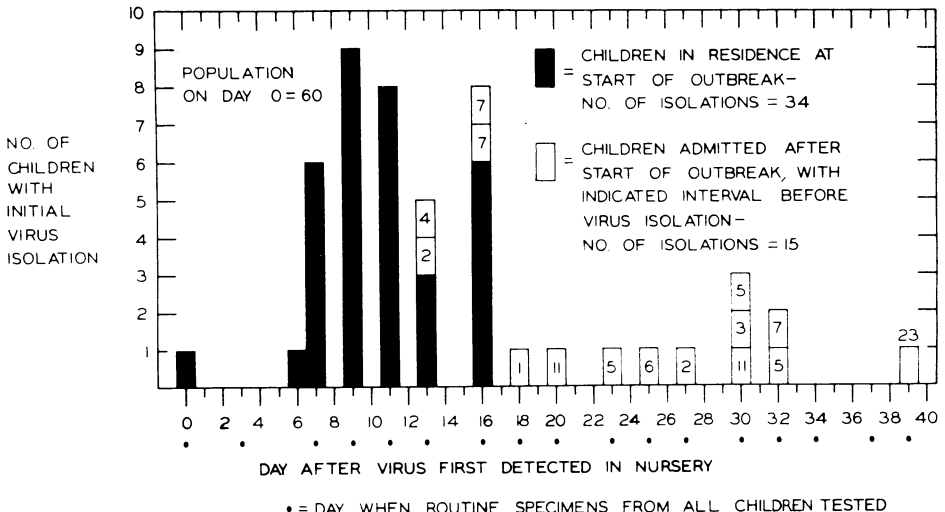


Figure 3—Temporal Distribution of Parainfluenza 3 Infection in Welfare Nursery Where Last Outbreak Occurred 12 Months Previously



(Reprinted from Chanock, R. M.; Bell, J. A.; and Parrott, R. H. Perspectives in Virology 2:126-138, 1961.)

**Table 4—Parainfluenza Neutralizing Antibody Status of Infants and Children from Several Age Groups**

Age (Mo)	% with Neutralization Antibody Titer 1:8 or Greater					
	Para 1		Para 2		Para 3	
	Number Tested	Per cent Positive	Number Tested	Per cent Positive	Number Tested	Per cent Positive
0-5	50	48	47	42	50*	60*
6-12	25	4	31	3	24	58
13-24	53	8	69	25	67	60
25-36	48	23	31	45	48	77
37-48	33	42	21	33	16	81
49->	31	74	39	59	0	—

\* 67% of 33 infants 0-3 mo and 47% of 17 infants 4-5 mo.

NOTE: Neutralization tests were performed with 10 TCD<sub>50</sub> of Type 1 and 100 TCD<sub>50</sub> of Types 2 and 3 viruses.

**Table 5—Reinfection with Parainfluenza 3 Virus in Three Outbreaks within Nine Months**

Previous Virus Recovery During Outbreak	Previously Infected Children Present During Subsequent Outbreak			
	Number 2		Number 3	
	Number Present	Virus Recovery	Number Present	Virus Recovery
No. 1	36	7	25	4
No. 2	—	—	14	2

(Adapted from Chanock, R. M.; Bell, J. A.; and Parrott, R. H. Perspectives in Virology 2:126-138, 1961.)

### Antibody Status by Age

The prevalence of parainfluenza viruses was also estimated by studying the neutralizing antibody status of serums from children in different age groups (Table 4). Neutralizing antibody for parainfluenza 1 virus, presumably transplacentally acquired, was present in 48 per cent of infants 0-5 months of age and 4 per cent of infants 6-12 months of age. The percentage of infants with antibody gradually increased with age thereafter so that about 74 per cent of children 4 years old or over had antibody. The

pattern was similar for parainfluenza 2 antibody although the percentage with antibody at 4 years of age was less than with parainfluenza 1. Sixty-seven per cent of infants 0-3 months of age had antibody to parainfluenza 3 virus. The percentage dropped to 47 per cent at ages 4-5 months, but neither at this age nor later was the percentage of children with antibody so low as that with parainfluenza 1 and 2. The percentage of children with antibody increased with advance in age. The fact that there was no period with virtual absence of parainfluenza 3 antibody further suggests that infection with this

virus is more frequent than that with the other two and must occur quite early in life. These data indicate that a large percentage of children, by the time they enter school, have been infected with these three parainfluenza viruses. Virtually all adults have antibody, at least to parainfluenza 1 and 3 viruses.<sup>7</sup>

**Spread of Infection in Closed Population**

An unusual opportunity to observe the spread of parainfluenza 3 infection in a nursery group occurred during the winter of 1958-1959 at the D. C. Junior Village, an emergency welfare domicile for children (Figure 3).<sup>7</sup>

When parainfluenza 3 infection first was detected in the nursery under surveillance, all but two of the 60 children had entered the residence since the previous outbreak. Occurrence of infection in time is shown in Figure 3. All infections in the original group except the first one occurred during a ten-day period. Infections detected during the subsequent period of 23 days occurred only in new arrivals at the nursery.

**Reinfection: Immunity**

The occurrence of three outbreaks within a nine-month period at this nursery also afforded an opportunity to assess whether or not reinfection with parainfluenza 3 virus is possible.<sup>7</sup> Table

**Table 6—Effect of Preinfection Neutralizing Antibody on Parainfluenza 3 Virus Recovery and Antibody Rise**

Preinfection Neutralizing Antibody Status (Reciprocal)	Neutralizing Antibody Rise		Virus Isolation	
	Number Tested	Per cent Positive	Number Tested	Per cent Positive
<8	46	100	27	96
8-32	22	91	15	67
64-1,024	50	34	37	33

(Adapted from Chanock, R. M.; Bell, J. A.; and Parrott, R. H. *Perspectives in Virology* 2:126-138, 1961.)

**Table 7—Effect of Preinfection Antibody on Frequency of Fever and Lower Respiratory Tract Illness During Parainfluenza 3 Outbreak**

Preinfection Neutralizing Antibody Status (Reciprocal)	Number Individuals Infected	Per cent Febrile Illness During Infection	Per cent Lower Tract Illness
<8	54	78	33
8-32	18	33	} 7
64-1,024	43	19	

(Adapted from Chanock, R. M.; Bell, J. A.; and Parrott, R. H. *Perspectives in Virology* 2:126-138, 1961.)

5 shows that it is. About one-fifth of the children infected during outbreak 1 also yielded virus during outbreaks 2 or 3. In two of 14 children who were virus-positive during outbreak 2 virus was also recovered during outbreak 3.

Data from some of these children also

show the effect of preexisting neutralizing antibody on reinfection as demonstrated by parainfluenza 3 virus recovery and antibody rise (Table 6).<sup>7</sup> Virtually all of the children with no preexisting antibody became infected. Low levels of antibody reduced the like-

**Table 8a—Proportion of Croup Illness Associated with Parainfluenza Infection in Various Studies**

Population			Virus Recovery				Serological Evidence of Infection					
Location	Age	Year	No. Tested	% Pos. Parainflu.				No. Tested	% Pos. Parainflu.			
				1	2	3	Total		1	2	3	Total
Wash., D.C. <sup>1</sup>	Inf., Ch.*	'57-61	206	20	4.4	4.4	29	154	21	8	10	40
Cincinnati <sup>2</sup>	Inf.	'55-56	12	—	16.6	—	16.6	11	—	45	—	45
Toronto <sup>3</sup>	Inf.	'55-56	15	—	66.6	—	66.6	—†	—	—	—	—
Wash., D.C. <sup>4</sup>	Inf., Ch.	'57-58	14	7.1	0	0	7.1	7	14.3	0	14.3	28.6
Moscow <sup>5</sup>	Ch.	'59	153	21.5	4.5	—	26	140	27.1	4.2	3.5	24.8
Melbourne <sup>6</sup>	Inf., Ch.	'59-60	227	23	0	8	31	—	—	—	—	—
Toronto <sup>7</sup>	Inf., Ch.	'60-61	155	47	0	4.5	51.5	—†	—	—	—	—

Collaborative Children's Hospital, D.C.—NIH Study, 1957-1961<sup>1</sup>; Chanock, 1956<sup>2</sup>; Beale, et al., 1958<sup>3</sup>; Kapikian, et al., 1960<sup>4</sup>; Bukrinskaya, et al., 1961<sup>5</sup>; Ferris, et al., 1960<sup>6</sup>; and McLean, et al., 1961.<sup>7</sup>

\* Inf. = Infant, Ch. = Child.

† Serologic studies performed only on individuals from whom virus was recovered.

**Table 8b—Proportion of Pneumonia Illness Associated with Parainfluenza Infection in Various Studies**

Population			Virus Recovery				Serological Evidence of Infection					
Location	Age	Year	No. Tested	% Pos. Parainflu.				No. Tested	% Pos. Parainflu.			
				1	2	3	Total		1	2	3	Total
Wash., D.C. <sup>1</sup>	Inf., Ch.*	'57-61	697	0.6	0.1	1.6	2	511	4	0.6	12	16
Wash., D.C. <sup>2</sup>	Inf., Ch.	'57-58	34	0	0	2.9	2.9	13	7.7	0	46	53.7
Moscow <sup>3</sup>	Ch.	'59	20	0	0	5	5	21	0	0	71	71
Newcastle <sup>4</sup>	Inf., Ch.	'59	—	—	—	—	—	48	2.1	4.2	0	6.3
London <sup>5</sup>	0-14 Yr	'59	—	—	—	—	—	33	—	—	—	7
	>15 Yr		—	—	—	—	—	86	—	—	—	3
Wisconsin <sup>6</sup>	Adult	'53-60	66	0	0	0	0	92	0	—	4.3	4.3

Collaborative Children's Hospital, D.C.—NIH Study 1957-1961<sup>1</sup>; Kapikian, et al., 1960<sup>2</sup>; Bukrinskaya, et al., 1960<sup>3</sup>; Gardner, et al., 1960<sup>4</sup>; Holland, et al., 1960<sup>5</sup>; and Evans, et al.<sup>6</sup>

\* Inf. = Infant, Ch. = Child.



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**Table 8c—Proportion of Bronchiolitis Illness Associated with Parainfluenza Infection in Various Studies**

Population			Virus Recovery				Serological Evidence of Infection					
Location	Age	Year	No. Tested	% Pos. Parainflu.				No. Tested	% Pos. Parainflu.			
				1	2	3	Total		1	2	3	Total
Wash., D.C. <sup>1</sup>	Inf. Ch.*	'57-61	321	1	0.3	4	5	227	1	0	12	13
Newcastle <sup>2</sup>	Inf., Ch.	'59	-	-	-	-	-	27	0	0	0	0
London <sup>3</sup>	Inf., Ch.	'59	-	-	-	-	-	32	0	0	0	0

Collaborative Children's Hospital, D.C.—NIH Study 1957-1961<sup>1</sup>; Gardner, et al., 1960<sup>2</sup>; and Holland, et al., 1960.<sup>3</sup>  
 \* Inf. = Infant, Ch. = Child.

**Table 8d—Proportion of Pharyngitis-Bronchitis Illness Associated with Parainfluenza Infection in Various Studies**

Population			Virus Recovery				Serological Evidence of Infection					
Location	Age	Year	No. Tested	% Pos. Parainflu.				No. Tested	% Pos. Parainflu.			
				1	2	3	Total		1	2	3	Total
Wash., D.C. <sup>1</sup>												
Hosp. Clinic	Inf., Ch.*	'57-61	706	1	0.4	2	3.2	521	4	2	13	19
	"	"	2,746	2.4	0.3	3	6	-	-	-	-	-
Wash., D.C. <sup>2</sup>												
Hosp. Clinic	Inf., Ch.	'57-58	23	4.3	0	0	4.3	7	0	0	43	
	"	"	79	1.3		2.5	3.8	13	0	0	23	
Newcastle <sup>3</sup>												
Hosp. Clinic	Inf., Ch.	'59	-	-	-	-	-	37	0	0	0	0
	"	"	-	-	-	-	-	28	3.6	3.6	-	7.2
London <sup>4</sup>	0-14 Yr	'59	-	-	-	-	-	52	-	-	-	9
	>15 Yr		-	-	-	-	-	24	-	-	-	0
Wis. URI <sup>5</sup>	Adult	'57-59	-	-	-	-	-	132	2.3		8.7	11
La., Miss. <sup>6</sup>	Adult	'58-59	875	2.6	-	-	2.6	-	-	-	-	-
N. C. <sup>7</sup>	Adult	'59-60	230	2.2	0.4	2.2	4.8	-†	-	-	-	-

Collaborative Children's Hospital, D.C.—NIH Study 1957-1961<sup>1</sup>; Kapikian, et al., 1961<sup>2</sup>; Gardner, et al., 1960<sup>3</sup>; Holland, et al., 1960<sup>4</sup>; Evans, et al., 1960<sup>5</sup>; Dick, et al., 1961<sup>6</sup>; and Bloom, et al., 1961.<sup>7</sup>  
 \* Inf. = Infant, Ch. = Child.

† Serologic studies performed only on individuals from whom virus was recovered.

likelihood of virus recovery but apparently allowed infection as manifested by an antibody rise in 91 per cent of subjects. Higher levels of antibody markedly limited but did not fully prevent reinfection.

Preexisting antibody also influenced

the likelihood and nature of clinical illness among those infected (Table 7).<sup>7</sup> Children with higher levels of antibody had a reduced frequency of fever during infection. Lower respiratory tract illness was present in 33 per cent of children with no preexisting antibody

but occurred in few children with any detectable neutralizing antibody.

Additional evidence that reinfection can occur, at least with parainfluenza 1 and 3 viruses, and that minor respiratory tract illness or a "cold" can result frequently from such reinfection has been shown among adult volunteers to whom these viruses were administered.<sup>8,9</sup> The studies at the D. C. Junior Village nursery and the human volunteer studies have also permitted the estimation that the incubation period for parainfluenza 1 virus infection is approximately from five to six days and for parainfluenza 3 infection, two or three days.<sup>7-9</sup>

## Comment

Whereas most of the reported studies have been carried out in children from the Washington, D. C., area it would seem surprising if parainfluenza virus infection were restricted to that age or that area. In fact, infection of children and adults has now been reported from many states and several countries. Table 8 is a compilation of findings of reported studies for parainfluenza infection in groups of ten or more individuals.<sup>2,10-21</sup> The studies of children tend to confirm the findings we have reported.<sup>11-17</sup> Several studies indicate that parainfluenza viruses are also playing a part in respiratory tract infection of adults. Dick recovered parainfluenza 1 virus from 2.6 per cent of military personnel with pharyngitis and bronchitis.<sup>20</sup> Bloom recovered parainfluenza 1, 2, or 3 viruses from 4.8 per cent of Marines with upper respiratory tract illness.<sup>21</sup> Evans found serologic evidence of infection with parainfluenza 1 virus in 2.3 per cent and parainfluenza 3 virus in 8.7 per cent of college students with upper respiratory tract illness.<sup>18,19</sup>

The accumulating evidence indicates that the parainfluenza viruses are im-

portant and prevalent agents; they contribute to both minor illness in children and adults and to some of the most severe respiratory tract illnesses in infants and children. Hypothetically, if an antigenically potent vaccine could be prepared for these agents and given to children just before they emerge from the period of protection by maternal antibody, a significant proportion of these severe illnesses in children could be prevented. It is even conceivable that frequent antigenic stimulus by a vaccine could produce a constantly high antibody level which would prevent reinfection and the colds that accompany reinfection with these viruses.

## Summary

The newly uncovered parainfluenza viruses are associated with a minimum of 6 to 19 per cent of respiratory tract illness in children. Parainfluenza 1, 2, or 3 viruses may be found in mild rhinitis, pharyngitis, and bronchitis but the more severe parainfluenza 1 and 2 infections seem to be associated with the croup syndrome and the more severe parainfluenza 3 infection to be associated with bronchopneumonia, bronchiolitis, or croup. Parainfluenza 1 and 3 infections occur in all seasons in each year. A vast majority of adults have been infected at least once. A child or adult may be reinfected with the same agent but the presence of antibody prevents severe illness and higher levels seem to lessen the likelihood of infection. An antigenically potent vaccine could prevent, theoretically, much serious respiratory tract illness in children and, frequently administered, might even reduce the colds that result from reinfection.

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Drs. Parrott, Vargosko, and Kim are associated with the Virology Section, Research Foundation of Children's Hospital of the District of Columbia, and the Georgetown University School of Medicine, Washington, D. C.; Dr. Bell is associated with the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.; and Dr. Chanock is associated with the Children's Hospital of the District of Columbia, the Georgetown University School of Medicine, and the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases.

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